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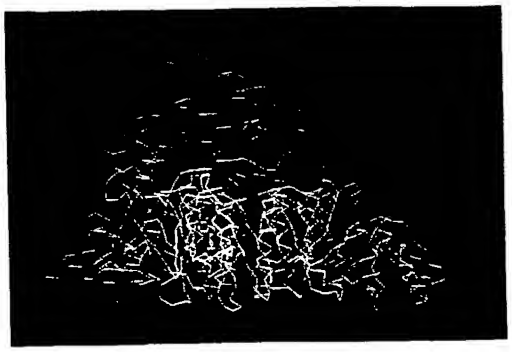
(54) Modification of pertussis toxin.

(57) The three-dimensional structure of crystalline pertussis holotoxin (PT) has been determined by X-ray crystallography. Crystal structures have also been determined for complexes of pertussis toxin with molecules relevant to the biological activity of PT. These three-dimensional structures were analysed to identify functional amino acids appropriate for modification to alter the biological properties of PT. Similar procedures may be used to predict amino acids which contribute to the toxicity of the holotoxin, to produce immunoprotective, genetically-detoxified analogs of pertussis toxin.

FIGURE 13



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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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(51) International Patent Classification 6 : C12N 9/64, C12Q 1/37 | A1

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(30) Priority Data:
08/261,582 17 June 1994 (17.06.94) US

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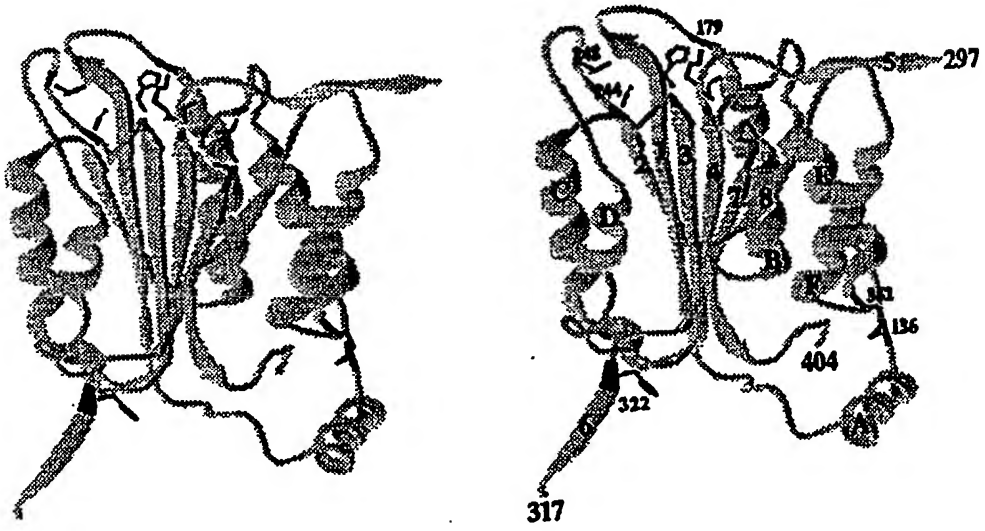
(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: CRYSTAL STRUCTURE AND MUTANTS OF INTERLEUKIN-1β CONVERTING ENZYME



(57) Abstract

Interleukin-1β converting enzyme ("ICE") processes an inactive precursor to the pro-inflammatory cytokine, interleukin-1β. The high-resolution structure of human ICE crystallized in complex with an inhibitor is determined by X-ray diffraction. The active site spans both the 10 and 20 kilodalton subunits. The accessory binding site is composed of residues from the p10 and p20 subunits that are adjacent to the two-fold axis of the crystal. The structure coordinates of the enzyme may be used to design novel classes of ICE inhibitors.

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(51) International Patent Classification 6 :
A61K 31/00, 38/00, C07K 14/525, 16/40, C12N 1/11, 1/13, 1/15, 5/10, 9/64, 15/57, 15/63, C12Q 1/37

A1

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(81) Designated States: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: TNF-α CONVERTING ENZYME

(57) Abstract

A metalloprotease that converts TNF-α from the 26kD cell form to the cell form to the 17 kD form has been isolated and purified and the cDNA sequence known. In particular, the protease has a molecular weight of approximately 80 kD. The isolated and purified protease is useful for designing an inhibitor thereof, and may find use as a therapeutic agent. Assays for detecting the protease-inhibiting activity of a molecule are also an aspect of the invention.

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C3H HB7E H642 H646 H650 H734
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Biol. Chem. Hoppe-Seyler, Vol. 376, June 1995, pages 385 to 388 Biosci. Biotech. Biochem., Vol. 57, No. 9, 1993, pages 1470 to 1476 Febs letters, Vol. 336, No. 3, 1993, pages 555 to 559 Journal of Chromatography, Vol. 568, No. 1, 1991, pages 55 to 68 Comp. Biochem. Physiol., Vol 96B, No. 2, 1990, pages 247 to 252 J. Biochem., Vol. 87, No. 4, 1980, pages 1133 to 1143

(58) Field of Search
UK CL (Edition O) C3H HB7E
INT CL[6] C12N 9/64
ONLINE: WPI, DIALOG/BIOTECH

(54) Production and purification of cathepsin L for X-ray crystallography

(57) Cathepsin L is a thiol protease and produced by cloning human epithelial cell DNA into E. coli using a secretion vector. The proenzyme is secreted into the periplasmic space of the E. coli and purified to a high specific activity (at least 40.000 nmoles/min/mg). The purified, correctly folded enzyme was crystallised and X-ray coordinates determined for use in rational drug design.

GB 2 306 961 A

The provisions of paragraph 3 of schedule 2 to the patents rules 1995 have effect in respect of this application,restricting availability of samples of specified micro-organisms to experts in accordance with those provisions.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

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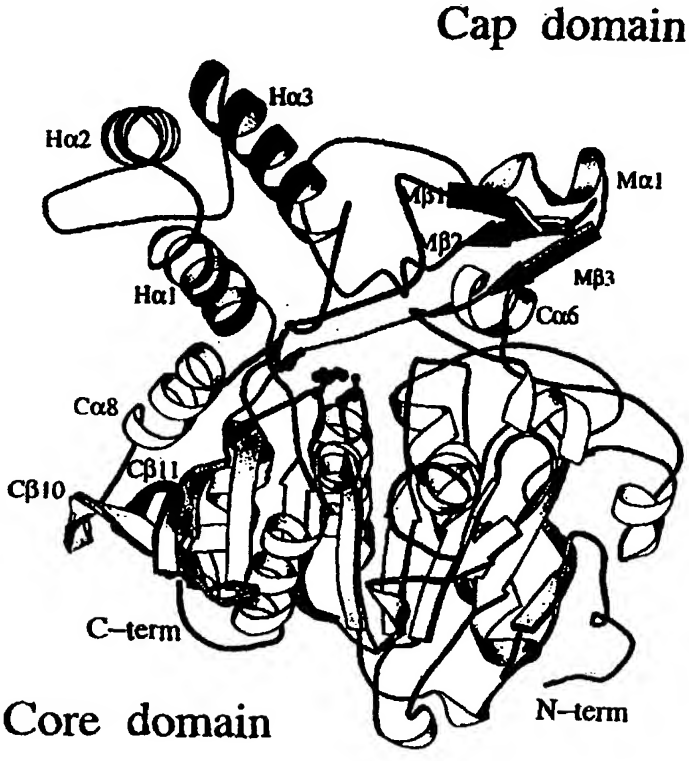
(74) Agents: FOX, Samuel, L. et al.; Sterne, Kessler, Goldstein & Fox P.L.L.C., Suite 600, 1100 New York Avenue, N.W., Washington, DC 20005-3934 (US).

(54) Title: PROTECTIVE PROTEIN/CATHEPSIN A AND PRECURSOR: CRYSTALLIZATION, X-RAY DIFFRACTION, THREE-DIMENSIONAL STRUCTURE DETERMINATION AND RATIONAL DRUG DESIGN

(57) Abstract

The present invention provides crystallized protective protein/cathepsin A (PPCA), a precursor thereof (pPPCA) or at least one subdomain thereof; methods for x-ray diffraction analysis to provide x-ray diffraction patterns of sufficiently high resolution for three-dimensional structure determination of the protein, as well as methods for rational drug design (RDD), based on using amino acid sequence data and/or x-ray crystallography data provided on computer readable media, as analyzed on a computer system having suitable computer algorithms.



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(51) International Patent Classification 6 : C12N 9/12, G01N 33/68 — A1

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(43) International Publication Date: 6 March 1997 (06.03.97)

(21) International Application Number: PCT/US96/13918

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(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

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(74) Agent: BERSTEIN, David, L.; Ariad Pharmaceuticals, Inc., 26 Landsdowne Street, Cambridge, MA 02139 (US).

(54) Title: CRYSTALLINE ZAP FAMILY PROTEINS

(57) Abstract

The invention relates to human ZAP-70, and in particular, to the region of ZAP-70 containing the tandem Src homology-2 ("SH2") domains, to crystalline forms thereof, liganded or unliganded, which are particularly useful for the determination of the three-dimensional structure of the protein. The three-dimensional structure of the tandem SH2 region of ZAP provides information useful for the design of pharmaceutical compositions which inhibit the biological function of ZAP and other members of the ZAP family of SH2 domain-containing proteins, particularly those biological functions mediated by molecular interactions involving one or both SH2 domains.

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(51) International Patent Classification 6 : A61K

A2

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(30) Priority Data:
08/620,663 26 March 1996 (26.03.96) US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: TUMOR NECROSIS FACTOR ALPHA CONVERTASE

(57) **Abstract**

The present invention relates to tumor necrosis factor alpha (TNFα), and more specifically to the enzyme TNFα-convertase (TNFα-con) that can proteolytically convert TNFα precursor to mature TNFα. The present invention provides DNA sequences encoding mammalian TNFα-con and functional equivalents thereof, recombinant expression vectors comprising said DNA sequences, host cell lines comprising said expression vectors, inhibitors of TNFα-con, inhibitors modified for use as ligands for affinity purification of TNFα-con, and methods for treating diseases or conditions resulting from abnormal levels of TNFα in a mammalian subject.